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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/691,504	10/18/2000	Marc K. Wallack	11221/5	5100
26646	7590	02/13/2004	EXAMINER	
KENYON & KENYON ONE BROADWAY NEW YORK, NY 10004			WEHBE, ANNE MARIE SABRINA	
			ART UNIT	PAPER NUMBER
			1632	

DATE MAILED: 02/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/691,504	Applicant(s) WALLACK ET AL.	
	Examiner Anne Marie S. Wehbe	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
 - If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
 - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
 - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 01 December 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 18-23,26,29-38,55-64,67,70-96,99 and 102-107 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 18-23,26,29-38,55-64,67,70-96,99 and 102-107 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 18 October 2000 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/1/03 has been entered. Applicant's amendment and response also filed on 12/1/03 has been entered. Claims 1-17, 24-25, 27-28, 39-54, 65-66, 68-69, and 97-98 have been canceled. Claims 18-23, 26, 29-38, 55-64, 67, 70-96, 99 and 102-107 are pending and under examination in the instant application. Please note however that the pending claims are still subject to the restriction/election requirement mailed on 3/26/02. In response to that requirement, the applicant elected for prosecution as a first species of immunostimulatory molecule IL-2, and as a second species of immunostimulatory molecule, IL-2, see applicant's response received on 10/1/02. The applicant is reminded that claims 18-23, 26, 29-38, 55-64, 67, 70-96, 99 and 102-107 have not been amended to recite the elected species of first and second immunostimulatory molecules, and that therefore these claims have only been examined to the extent that they read on the elected species of IL-2 as the first and second immunostimulatory molecule. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in previous office actions.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows: the specification does not contain a specific reference to provisional application 60/240,933 in the first sentence of the specification. An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78(a)(2) and (a)(5)).

Claim Rejections - 35 USC § 112

The rejection of claims 18-23, 26, 29-38, 55-64, 67, 70-96, 99, and 102-107 under 35 U.S.C. 112, first paragraph, for scope of enablement is withdrawn in view of applicant's amendments to the claims.

However, please note that examination of the claims for patentability under 35 U.S.C. 112, first paragraph, has been based on the elected species of IL-2 as the first and second immunostimulatory molecules since the generic claims have not been found allowable.

The rejection of claims 56-59 and 80-81 under 35 U.S.C. 112, second paragraph, for indefiniteness regarding the term "about" is withdrawn in view of applicant's amendments to the claims.

Claims 18-23, 26, 29-38, 55-64, 67, 70-76 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 18 contains a grammatical error which renders the claim confusing. Claim 18 as amended recites, “wherein the antigen presenting cells are dendritic cells and/or a monocytes” (emphasis added). Monocytes are a plural form of monocyte and thus “a monocytes” is confusing in terms of the metes and bounds of the claims. It is suggested that applicant’s delete “a” in front of monocytes in order to overcome this rejection. Note that claims 19-23, 26, and 29-38 depend on claim 18 and thus have been included in this rejection.

Claim 22 lacks antecedent basis for , “ the second recombinant vaccinia virus”. Claim 22 depends on claim 18, which does not recite a second recombinant vaccinia virus. It is suggested that the applicant amend claim 18 in step(b) to recite that the cancer cells are infected with a second recombinant vaccinia virus in order to overcome this rejection.

Claim 38 lacks antecedent basis for “ the composition”. Claim 38 depends on claim 18 which does not recite a “composition”. It is suggested that applicant’s amend claim 38 to recite “treated with the vaccine” instead of “treated with the composition” in order to overcome this rejection.

Claim 55 contains several typographical/grammatical errors which render the claims confusing such that the metes and bounds of the claim cannot be determined. In step (b), the claim has been amended to recite “ wherein the antigen presenting cells **area** dendritic cells and/or a monocytes” (emphasis added). It is unclear what is meant by “area”. It is suggested that the applicant amend the claim to recite “are dendritic cells...”. In regards to “a monocytes”,

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monocytes are a plural form of monocyte and thus “a monocytes” is confusing. It is suggested that applicant’s delete “a” in front of monocytes in order to overcome this rejection. Further in step (b), the claim recites , “.... cancer cells, as infected with a second.....” (emphasis added). The use of the word “as” in this context is confusing such that the metes and bounds of the claim cannot be determined. It is suggested that the applicant delete the word “as” in order to overcome this rejection. Note that claims 56-64, 67, and 70-77 depend on claim 55 and thus have been included in this rejection.

Claim Rejections - 35 USC § 103

The rejection of claims 18-23, 26, 29-38, 55-64, 67, 70-96, 99, and 102-107 under 35 U.S.C. 103(a) as being unpatentable over Nestle et al. (1998) Nat. Med., Vol. 4, No. 3, 328-332 in view of Sivanandham et al. (1994) J. Immunol. Immunother., Vol. 38, 259-264, is maintained. Applicant’s arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

The applicant arguments are essentially the same as those presented in the previous response and addressed in detail in the final office action mailed on 7/1/03. The applicant’s arguments were not found persuasive previously and have not been found persuasive now for the same reasons of record discussed in the 7/1/03 action and below.

The applicant argues that neither Nestle et al. nor Sivanandham et al. teach a 2-part vaccine as recited in the instant claims. Therefore, the applicant concludes that the combination

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of references fails to teach or suggest the claimed invention and involves improper hindsight reasoning on the part of the examiner. In response, it appears that applicants are arguing that the cited references do not expressly suggest the claimed invention. However, it is well established in case law that a reference must be considered not only for what it expressly teaches, but also for what it fairly suggests. *In re Burkel*, 201 USPQ 67 (CCPA 1979). Furthermore, in the determination of obviousness, the state of the art as well as the level of skill of those in the art are important factors to be considered. The teaching of the cited references must be viewed in light of these factors. It is further noted that the test for combining references is not what the individual references themselves suggest, but rather what the combination of disclosures taken as a whole would have suggested to one of ordinary skill in the art. *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). For the purpose of combining references, those references need not explicitly suggest combining teachings, much less specific references. *In re Nilssen*, 7 USPQ2d 1500 (Fed. Cir. 1988). The examiner further recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge

gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In the instant case, Nestle et al. was cited for teaching methods of vaccinating human patients with patient-derived dendritic cells pulsed with melanoma tumor lysate, wherein 10X6 tumor lysate pulsed dendritic cells are injected into inguinal lymph nodes, and wherein the dendritic cells express at least 2 HLA class I A antigens (Nestle et al., page 328, and page 329, Table 1). Applicant's comment that the dendritic cells of Nestle et al. are cultured *in vitro* in the presence of IL-4 and GM-CSF are not relevant to the claims under examination which do not place any limitations on derivation of the dendritic cells. Likewise, the applicant's arguments regarding KLH are moot since the claims do not exclude the inclusion of other substances in the claimed vaccines.

The previous office actions further acknowledged that Nestle et al. differs from the instant invention by not teaching that the dendritic cells are pulsed with tumor lysate from tumors infected with VV-IL2, or that the pulsed dendritic cells are administered with separate VV-IL-2.

Sivanandham et al. was cited to supplement Nestle et al. by teaching that vaccinia oncolysate prepared from VV-IL-2 infected colon tumor cells is superior to oncolysate alone in generating anti-tumor immune responses (Sivanandham et al., page 262, Figures 3 and 4). Motivation to combine the teachings of Nestle and Sivanandham is found in Sivanandham's teaching that vaccinia oncolysate prepared from VV-IL-2 infected colon tumor cells is superior to oncolysate alone in generating anti-tumor immune responses. Thus, based on the motivation provided by the teachings of Sivanandham et al., that oncolysate prepared from tumor cells

infected with VV-IL-2 is more immunogenic, it would have been *prima facie* obvious to the skilled artisan to substitute vaccinia oncolysate prepared from VV-IL-2 infected tumor cells for the uninfected tumor lysate taught by Nestle et al. in Nestle's methods of treating tumors by administering DCs pulsed with tumor lysate. Based on the increased efficacy of the lysate taught by Sivanandham et al. in inducing immune responses, the skilled artisan would have had a reasonable expectation of success in generating anti-tumor immune responses *in vivo* by administering dendritic cells pulsed with vaccinia oncolysate prepared from VV-IL-2 infected tumor cells.

Sivanandham et al. was further cited for teaching that the co-administration of viral oncolysate and exogenous IL-2 improves immune responses compared to the administration of viral oncolysate alone (Sivanandham et al., page 262, Figure 3). While Sivanandham et al. teaches the administration of recombinant IL-2 with viral oncolysate, the skilled artisan would have been motivated to use the VV-IL-2 also taught by Sivanandham instead of the recombinant IL-2 to limit systemic IL-2 toxicity and to prolong the exposure of the mammal to IL-2, since Sivanandham teaches that recombinant IL-2 has a short half-life and causes toxicity in humans (Sivanandham et al., page 260, column 1). The skilled artisan would have had a reasonable expectation of success in using directly injected VV-IL-2 to stimulate immune responses based on the data presented by Sivanandham et al. that direct injection of 2×10^6 pfu of VV-IL-2 decreases tumor burden compared to controls (Sivanandham et al., page 262, Figure 3). Thus, it would have been *prima facie* obvious to the skilled artisan at the time of filing to supplement the administration of DCs pulsed with vaccinia oncolysate with the direct administration of VV-IL-2 in order to increase anti-tumor immune responses. Based on the teachings of Sivanandham et al.

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that IL-2 improves immune responses to oncolysate, and that VV-IL-2 induces anti-tumor immune responses, the skilled artisan would have had a reasonable expectation of success in generating anti-tumor immune responses by combining the administration of DCs pulsed with vaccinia oncolysate prepared from VV-IL-2 infected tumor cells with the administration of VV-IL-2. The applicant is further reminded that obviousness does not require absolute predictability of success; for obviousness under 35 U.S.C. § 103, all that is required is a reasonable expectation of success. See *In re O'Farrell*, 7 USPQ2d 1673 (CAFC 1988).

Therefore, for the reasons of record as discussed above and in previous office actions, the rejection stands.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. The examiner can be reached Monday- Friday from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Amy Nelson, can be reached at (571) 272-0804. For all official communications, the technology center fax number is (703) 872-9306. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
-PRIMARY EXAMINER

